THE MODERN ASPECT OF INDICANURIA,

WITH SPECIAL REFERENCE TO THE RELATION BETWEEN INDICAN AND THE ACIDITY OF THE GASTRIC JUICE.

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The earliest announcement of the discovery of indigo in an animal excretion was made by Prout (*Nature and Treatment of Stomach and Urinary Affections*, third edition, London, 1840, p. 96; see also fifth edition, 1848, p. 567) in 1840.

Urines colored blue to a greater or less extent, as well as blue sediments, it is true, had been described long before Prout's days, but the nature of the coloring had not been definitely established.

The earlier literature from the times of Hippocrates and Galenus has been compiled by Martin (Heller's *Archiv*, 1846, p. 191).

Actuarius ("De Urinis," quoted by Willis, *Urinary Diseases*, p. 139) toward the end of the 13th century records an instance of slate-colored urine under the name of "Urina Veneta," and Janus Planeus (*Ibid.*, p. 131) in 1767 describes under the same title the urine of a man of sixty which deposited on standing a deep ultramarine blue sediment.

The first definite attempt at analysis of such blue coloring-matter was made by Julia Fontanelle (*Arch. Gén. de Méd.*, 1823) in 1821, the results being published in 1823. The patient, affected with an acute disease of the " urinary tract, aged eighty-two years, passed urine on the second day of the disease which was of a marked blue color, and deposited a filamentous sediment of the same color on standing.

The results of his analysis Fontanelle states as follows: The urine contained but little urea, much albumin, what he calls "gelatine," probably meaning mucus, and hydrocyanate of iron united to sodium as a triple salt, to which he refers the blue color of the urine. He admits, however that the amount of urine at his disposal was not sufficient for the purpose of a complete analysis.

Braconnot (*Journ. de Chim. Méd. de Pharm. et de Toxicol.*, 1845, vol. i. p. 569; see also *Annal. de Chim. et de Physique*, 2d series, vol. xxix. p. 252), in 1845, states that twenty years ago he had occasion to examine a urine in which a fine blue substance, looking like Prussian-blue, was suspended. This pigment he called cyanourine. In the same article Braconnot also describes a green urine, and attempts to prove the identity of the coloring-matter in this case with his cyanourine, imagining the green color to result from a mixture of the yellow color of normal urine with a small amount of the blue cyanourine.

Spangenberg (Schweigger's *Journal*, vol. xlvii. p. 487), Garnier, and Delens (*Ibid.*, vol. xxiii. p. 262; see also *Journal de Méd.*, vol. lxxii. p.

174) describe a similar pigment, which Simon (Simon's *Beiträge zur Physiol. und Pathol. Chemie und Microscopie*, Berlin, 1843, vol. i. p. 118), however, wishes to be distinguished from Braconnot's and each other.

Julia Fontanelle (*Journal de Chimie Méd.*, 1845, vol. i. p. 341) in 1845 first found Prussian-blue, or the sesqui-ferrocyanide of iron in the urine of a boy laboring under severe colic, attributed to his having swallowed a quantity of ink. The blue deposit continued for a day or two after the attack, leaving the urine a natural color, but containing some soluble cyanide, as a blue precipitate was produced upon the addition of an iron salt. Several other instances of Prussian-blue deposits have occurred, and it is remarkable that in most of these iron has been accidentally or intentionally taken. These deposits are said to be artificially produced by giving to a patient who has been taking some preparation of iron a few doses of ferrocyanide of potassium.

In the same year Velsen (*Prager Vierteljahrsch.*, vol. v. p. 109) mentions the occurrence of a dark violet urine which he observed in a man aged eighty-four years, suffering with chronic cystitis, following or associated with the taking of milk and lime-water. Unfortunately a chemical examination was not made.

In 1840 then, Prout (*loc. cit.;* see also Dr. O. Rees on the *Analysis of Blood and Urine*, London, p. 81) for the first time demonstrated the occasional occurrence of indigo in the urine. His patient was a middle-aged person of a neurotic temperament. He was in the habit of taking Seidlitz powders, and the indigo most generally appeared in the urine in the form of a dark-blue sediment, after he had taken one of these powders. On one occasion the quantity was so large that it could be collected and examined, when it was found to possess all the properties of indigo, and was obtained in a state of purity by sublimation. Prout says that he expected the blue pigment to consist of Prussian-blue.

In 1845 Heller (Heller's *Archiv für Physiol. und Pathol. Chemi. und Microscop.*, 1845, p. 161; *Ibid.*, 1844, p. 14, and 1846, pp. 19, 536, and 539) found a substance in the urine of cholera patients, and later also in normal urines, which he termed uroxanthine, and which can be broken down into a blue and a red pigment, termed uroglaucine and urrhodine respectively, both of a crystalline nature.

Martin (Heller's *Archiv*, 1846, p. 191) in 1846 further describes a blue pigment, urocyanine, in the urine in various diseases, associated with what he terms "a deficient decarbonization of the blood."

Scherer (*Annal. d. Chemie und Pharmacie*, 1846, vol. lvii. p. 180) in the same year expressed the opinion that the blue color obtained by boiling urine with muriatic acid is referable to a decomposition-product of the normal urinary pigment.

In 1847 Virchow next mentions a blue urine which he himself had observed in the case of a weakly boy, suffering with vesical pains and incontinence. Freshly voided, the urine was very pale and slightly yellow, and only deposited small blue flocculi when exposed to the air. These flocculi, microscopically examined, consisted of indigo-blue, radiant needles, which underwent no change upon micro-chemical treatment. This pigment he termed "Harnblau."

Later, in 1854, Virchow (*Arch. für Path. Anat.*, 1847, vol. i. p. 423, and vol. vi. p. 259; see also Würzburg, *Verhandl.*, vol. ii. p. 303) states that he has met with the same substance on treating the urine of an almost famished man with mineral acids.

In 1855 Hill Hassall (*Philosoph. Magaz.*, September, 1853, referred to in *Prager Viertelj. f. d. prakt. Heilk.*, 1855, vol. xlvi., *Analekten*, p. 73) describes a urine which he observed in 1852, in which, after standing for three or four days, a film had formed upon the surface, which at first presented a slate color, but later turned into a deep blue. Microscopically, this film was seen to consist of the usual "vibrios," triple-phosphate crystals, and a large number of dark or light grayish particles. Gradually this blue pigment disappeared from the urine. The extracted coloring-matter presented all the characteristics of indigo. Hassall later on repeatedly observed the same pigment in urines, obtaining the same at times in the form of a voluminous precipitate, at others in quantities only recognizable by the microscope. He imagines the indigo in the urine to result from the oxidation of a brown pigment which he observed in the same urine, and which he regarded as a derivative of hæmatine. The urines from which the indigo was obtained were mostly of a light straw color, alkaline in reaction, of a low specific gravity, and readily became turbid; none of the cases, however, were cases of Bright's disease. Its occurrence Hassall regards as pathological.

V. Sicherer (*Annal. d. Chem. und Pharm.*, 1854, vol. xc. p. 1) obtained indigo-blue from an apparently normal urine on boiling with a mineral acid. The identity of indigo-blue with the coloring-matter described as cyanourine, Sicherer thinks cannot be definitely excluded.

Virchow (*Arch. f. Path. Anat.*, vol. vi., *loc. cit.*) also expresses the view that the "Harnblau" probably never exists preformed in the urine, but that it appears after exposure to the air, in consequence of the decomposition of its mother-substance, or upon boiling with mineral acids, preferably muriatic acid, when gradually, on standing, a violet, brownish, or black sediment appears, which may or may not be crystalline. Virchow in short appears to imagine a direct relation to exist between his "Harnblau" and the blood pigment.

In 1854 Gubler observed the blue color resulting from the addition of nitric acid to albuminous urine, and thought the pigment formed to be a derivative of indigo. He found this pigment in cases of cholera, typhoid fever, smallpox, scarlatina, acute albuminuria, and especially abundant in choleriform diarrhœa and cholera Asiatica, and also taught that prognostic conclusions could be drawn from the intensity of the reaction. (See Schmidt's *Jahresb.*, 1859.)

Thus stood matters in 1857, when Schunck (*Mem. of Lit. and Phil. Soc. of Manchester*, vol. xiv. p. 239; *Phil. Mag. and Journal of Sc.*, 4th series, vol. xiv. p. 288. See also *Chem. Cbl.*, 1857, p. 957, and *Jahresb. d. Chem.*, 1855, p. 659; 1857, p. 564; 1858, p. 465) demonstrated the constant presence of a substance in the urine which yields indigo-blue on boiling with mineral acids or when undergoing a certain decomposition upon exposure to the air. This substance he called indican, and thought the same to be identical with vegetable indican, obtained from certain plants, such as the indigofera tinctoria, isatis tinctoria, etc.

Since that time blue urines and blue sediments have been repeatedly observed.

Wyss (*Arch. f. Heilkunde*, 1863, vol. ix. p. 235) thus describes the occurrence of a dark brownish-violet color in urine voided immediately after an attack of cholera, after having stood exposed to the air until ammoniacal decomposition had set in. The same result was obtained on boiling such urines with mineral acids, which fact had been already demonstrated for almost any urine to a greater or less extent by Heller in 1844, as set forth above, and by Middledorpf (Günzburg's *Ztschf. f. klin. Med.*, 1852, p. 65) in 1849.

Frerichs (*Die Bright's che Nierenkrankheit*, 1851, p. 191), Begghby (*Monthly Journal*, October, 1852, cit. by Güterbock in *Der Deutsch. Klinik*, 1852), Güterbock (*Deutsch. Klinik*, 1853), Buhl (*Ztsch. f. rationelle Med.*, N. F., 1855, vol. vi. p. 1), Gubler (*Gaz. Méd. de Paris*, December, 1854), Lindsay and Osborne (*Medical Times and Gazette*, March, 1855, cited by Thudichum, *Ninth Report of the Medical Officer of the Privy Council*, 1866, London, 1867, p. 468), Thudichum (*l. c.*), and Lehman ("Chem. und physik. Studien über die Cholera," Dissertation, Zürich, 1857) had made the same observations in choleraic urines.

Brudeberger (Virchow's *Archiv*, vol. xxxviii. p. 310) claimed to have demonstrated the presence of biliary coloring-matter in cholera urine, by treating the same with nitric acid, a fact which was doubted, however, by Buhl (*l. c.*) and Frerichs (*l. c.*); and Gubler (*Gaz. des Hôp.*, 1866, No. 104, p. 410) expresses the opinion directly that the color-play referred to must be referable to indigo. Thudichum (*l. c.*) finds that on boiling cholera urine with mineral acids a certain substance is split up into a blue and a red pigment, choleraic urorubine, and choleraic urocyanine, calling the mother-substance choleraic urocyaninogen. In other words, Thudichum here expresses under different names a fact which had already been established by Heller twenty-two years before, and, like Heller, he did not recognize the identity of his choleraic urocyanine (Heller's uroglaucin) with indigo. Wyss (*l. c.*) also demonstrated the incorrectness of Brudeberger's observations, and succeeded in definitely demonstrating the true nature of the blue coloring-matter obtained from cholera urine, recognizing this to be indigo, derived from the indican of Schunck.

While Wyss had thus established the identity of Thudichum's choleraic urocyaninogen with indican, and that of choleraic urocyanine with indigo, Kletzinsky (*Wiener med. Woch.*, 1859, No. 27, cited by Thudichum in his *Pathology of Urine*, p. 326) had done the same with Heller's uroglaucin, also proving the identity of Heller's urrhodine with the indigo red of Berzelius, and Schunk that of Heller's uroxanthine with indican.

In 1858 and 1859 Carter (*Edinburgh Med. Journal*, July, 1858, p. 86, vol. iv., part 1, and 1859, vol. v. p. 119) succeeded in establishing the constant presence of indican in health as well as in disease, having examined the urines of 300 persons in this direction.

He fully coincides with Heller in regarding indican as a physiological and constant constituent of human urine.

The reason why Hassall regarded indican as a pathological constituent of the urine, Carter refers to the putrefactive method employed by the former.

Schunck established the presence of indican in 39 out of 40 normal urines.

From this period on the occurrence of blue urines and blue sediments need not occupy our attention any longer, and it will suffice to append here a short *résumé* of the literature upon the subject up to date.

Gilchrist (*Edinburgh Med. Journal*, 1862; see also *Allgem. Med. Central Ztg.*, 1862, and *Prager Viertelj. f. d. prakt. Heilk.*, 1863, vol. lxxvii., *Analekt*, p. 14) in 1862 cites the case of a woman, aged fifty-eight years, suffering with rheumatism for many years; her urine was of a dark greenish-yellow color, ammoniacal, and deposited a bluish-green sediment consisting of triple phosphates, epithelial cells, and amorphous yellowish-brown, and light and dark blue particles. This pigment Gilchrist regards as indigo-blue. He also refers to a case of indigosuria recorded by Beale.

Beneke (*Pathol. d. Stoffwechsels*, Berlin, 1874, p. 185) in 1874 mentions a blue urine that was passed by a case of chronic Bright's disease associated with general anasarca, the blue color however only appearing on certain days.

Beneke also refers to one case of indigosuria in which the blue coloring-matter was recognized as indigo by Debuque (cited by S. Parkes: *The Composition of the Urine*, London, 1860, p. 197).

A very interesting case was reported in 1888 by Kahler (*Prager med. Woch.*, 1888, p. 543), who observed in the urine of a patient, aged seventy-six years, the subject of a unilateral pyonephrosis (pyelitis) of many years' standing, the formation of a bluish-red film on the surface, with a sediment that was full of blue coloring-matter, the walls of the vessel being likewise covered with the same. The urine was ammoniacal, and emitted a mild odor of sulphuretted hydrogen. The blue coloring-matter in the sediment occurred in both amorphous and crystalline form, and was recognized as indigo. The indigosuria in this case always appeared paroxysmally, and was accompanied by hydrothionuria. That hydrothionuria is the result of bacterial activity was shown by Müller (*Berliner klin. Woch.*, 1887, Nos. 23 and 24), and the simultaneous occurrence of indigo and sulphuretted hydrogen would make it appear very probable that the former arises under the same or similar conditions as the latter, a supposition which is very strongly supported by the observations of Alvarez (*Comptes rend. d. l'Académie des Sciences*, 1887, vol. cv. p. 286). The indican in this case was never found to be increased, but rather diminished, in quantity.

A similar case was observed by V. Udránszky and published by Plosz (*Zeitsch. f. physiol. Chemie*, vol. vi. p. 504, and vol. viii. p. 86), in which the urine was ammoniacal, and contained free indigo and sulphuretted hydrogen, the case being one of ulcerative cystitis with pyelitis and nephritis. A red pigment was also noticed in crystalline form, the chromogen of which is frequently associated with indican in normal and pathological urines. In Kahler's case there were no red crystals observed, but a red pigment could be extracted, which Kahler thinks identical with that obtained by Udránszky and Plosz.

In 1880 Litten (*Central. f. d. Med. Wiss.*, 1880, p. 823) reported a case of infiltrating carcinoma of the liver with simple round ulcers of the stomach, in which death resulted from gastro-intestinal hemorrhage. The urine at first was icteric, but later became a dark blue violet, without doubt referable to indican.

Ultzmann ("Neuropathien des männlicken Harn und Geschlechtsapparates;" *Wiener Klinik*, 1879, p. 120. "Harnconcretionen des Menschen und die Ursachen ihrer Entstehung." Wien, 1882) observed a violet-colored urine with markedly blue sediments in a fatal case of peritonitis; he furthermore mentions the case of a tabetic with vesical paresis, in which blue sediments were seen for a long time and suddenly disappeared; the same patient suffered with temporary glycosuria without other diabetic symptoms. The same observer also states that urates, especially the ammonium urate, are very apt to carry down indigo and appear blue or violet colored, and that indigo is not infrequently found in traces, at least, in urinary calculi. Concretions containing a larger amount of indigo, however, and which might properly be called indigo calculi, are of decided rarity. In the literature, as far as I have been able to find, only two cases of indigo calculi have been reported. Ord (*Trans. Path. Soc. of London*, 1878, vol. xxix. p, 155) thus records an instance in which a stone obtained from the pelvis of the right kidney weighed 2.6 grammes, consisting of coagulated blood, and phosphates, but to the greatest extent of indigo. The left kidney in this case was the seat of a round-celled sarcoma which also occluded the left ureter, producing dilatation of the pelvis and calices, which were filled with pus and a branching phosphatic calculus.

The second case of this kind was reported by Chiari (*Prager med. Woch.*, 1888, p. 541), where concretions were discovered in both kidneys, consisting to a large extent of indigo, with an albuminous basis and a small amount of phosphates. The patient, a female of thirty-four years, had had attacks of renal colic for five years off and on, and in the urine pus and smaller concretions had been repeatedly observed.

Ord (*l. c.*) explained his case by assuming that the formation of pus in the left kidney and the retention of decomposing pus constituted the source of increased indol-formation, resulting in an increased elimination of indican by the right kidney, where, coming into contact with the acid urine in the healthy right kidney-pelvis, indigo would be set free, leading to the formation of a stone.

Chiari also looked upon the bilateral suppurative pyelitis as the *primum mobile*, but regards the setting free of indigo as the result of microbic activity upon the indican.

A blue urine was further reported by A. Robin (*Compt. rend. de la soc. de Biol.*, 1875) in 1875, coming from a case of hysteria. The blue pigment in this case Robin, upon chemical examination, regards as identical with Braconnet's cyanourine, and definitely denies its identity with indigó.

V. Jaksch (*Diagnostik*) states that indigo was found to be present in remarkable abundance during the process of ammoniacal fermentation in the urine of jaundice, from a patient with hypertrophic cirrhosis of the liver. Numerous indigo-crystals, of which v. Jaksch gives an excellent representation, were also found by him in a case of hepatic abscess, in the sediment of the urine.

I myself have not infrequently observed the presence of indigo in the urine, often coloring epithelial cells and leucocytes, in cases of chronic interstitial nephritis, while in decomposing urines traces at least can be found in almost every specimen. It has thus been seen that blue urines and blue sediments have been known to occur since time immemorial, and that any urine when treated with mineral acids will permit of the extraction of a blue coloring-matter, which has received different names by different observers, viz., Prussian-blue, urocyanine, cyanourine, harnblau, uroglaucine, choleraic urocyanine, and which upon more detailed examination has been definitely demonstrated to be indigo-blue, being one of the products of decomposition and oxidation of a colorless mother-substance, present in every urine to a greater or less extent, which had been named indican by Schunck, its discoverer, and which has been shown to be identical with the uroxanthine of Heller and Thudichum's choleraic-urocyaninogen.

The experiments of Schunk were fully confirmed by Hoppe-Seyler (Virchow's *Archiv*, 1863, vol. xxvii. pp. 388–392) in 1863, who demonstrated the constant presence of indican in over a hundred human urines, and also in such of carnivora and herbivora. Its formation Hoppe-Seyler regards as a probable function of the kidneys, since in his examinations of the spleen, liver, pancreas, muscles, blood, and kidneys traces were only found in the latter organs.

The same observer also mentions the occurrence of a large amount of indican in a brown urine obtained from an individual afflicted with a melanotic carcinoma of the orbit.

While Schunck, however, regards indican as a glucoside and as identical with vegetable indican, a view against which Hoppe-Seyler had already spoken, Baumann was the first to demonstrate that no sugar is formed in the process of decomposition of animal indican, but sulphuric acid and a compound belonging to the indigo-group, which had been previously found as one of its products of decomposition by Nencki (Baumann: *Ber. der Deutsch. chem. Gesellsch.*, vol. ix. p. 54; Pflueger's *Archiv*, vol. xiii. p. 307; *Zeitsch. für physiol. Chemie*, vol. i. p. 60); and in 1879 Baumann, in conjunction with Brieger (*Zeitsch. für physiol. Chemie*, vol. iii. p. 254; *Ber. der Deutsch. chem. Gesellsch.*, vol. xii. p. 2166) and Thiemann (*Ber. der Deutsch. chem. Gesellsch.*, vol. xii. p. 1098; *Ibid.*, p. 1192; *Ibid.*, vol. xiii. p. 408), was able to demonstrate that urinary indican is a combination of the conjugate sulphate of a hydroxylated indol with an alkali, which they termed indoxyl-sulphate, the term indican to be restricted to the indigo-yielding substance of plants, viz., Isatis tinctoria, etc.

In the meantime indol had been shown to be the mother-substance of the indigo-group by Baeyer. Kuehne (Virchow's *Archiv*, vol. 39) had found a substance among the ultimate products of albuminous digestion by means of pancreatic juice, which he regarded as indol, and Radziewsky (Dubois-Reichert's *Archiv*, 1870, Heft i.) showed indol to be a normal and constant constituent of the feces, to which in part the disagreeable odor of the latter is due, so that it was not unnatural for Jaffe (Pflueger's *Archiv*, vol. iii. p. 448) to express the idea that the indol formed in the intestines should be regarded as the source of the urinary indican and the indigo obtained therefrom.

The proof for this view was brought forth by the experiments of Masson ("Des matières colorantes au point de vue physiologique;" Dissertation, Berne, 1874) in 1874, who, working under Nencki, found that the elimination of indican is increased in rabbits after subcutaneous injections of indol, an observation which was confirmed later on by Jaffe, and not originally made by him, as is usually stated.

The question now naturally arises, How is indol produced? and it is Nencki especially (*Ber. der Deutsch. chem. Gesellsch.*, vol. ix. p. 1593) to whom we are indebted for the solution of this problem. In 1874 he found indol to be a normal product of intestinal digestion, and expressed the view that its formation was the result of bacterial activity.

Koukol-Yasnopolsky (Pflueger's *Archiv*, vol. xii. p. 78) confirmed Nencki's work and found indol to be a constant product of albuminous putrefaction in alkaline media.

In a later communication Nencki (*Ber. der Deutsch. chem. Gesellsch.*, vol. ix. p. 299) definitely declares indol to be a specific product of albuminous putrefaction in the presence of organized ferments, in accordance with which Kuehne and Huefner find that no indol is formed when albuminous material is digested with pancreatic ferments in the absence of putrefactive processes.

Salkowsky (*Ber. der Deutsch. chem. Gesellsch.*, vol. ix. p. 408), on the strength of experiments made by Hoppe-Seyler and his pupils (Tuebinger, *Med. Chem. Untersuchungen*, vol. iv.; Pflueger's *Archiv*, vol. xii. p. 1), in which the formation of indol was observed from albuminous material kept under ether, thinks that the non-organized ferments, as well as the organized, are capable of causing the formation of indol, and that the intestinal tract is hence not the only source of the indican of urine, but that the body-tissues must be regarded as a second source of its formation.

That the experiment of Hoppe-Seyler, referred to, and hence the views of Salkowsky are erroneous, the former being probably referable to some technical errors, is proved by the following facts: According to Senator (*Zeitsch. für physiol. Chemie*, vol. iv., 1880), indican does not occur in the urine of newly born infants which have not as yet received nourishment, a point strongly in favor of Nencki's teachings, putrefiable substances being present, but no putrefactive organism, an observation moreover with which the chemical composition of meconium stands in perfect accord.

Tuczek's (*Neurologisches Cbl.*, 1884, p. 307; *Arch. für Psych. und Nervenkrankh.*, vol. xv. Heft 3) observations on abstinence in cases of insanity, where indican was only then observed in the urine, when albumin, even in minimal amounts, was ingested, but was otherwise absent, also speaks strongly against Salkowsky.

There should also be mentioned a case of Dr. Rabbas, reported by Mueller: A patient, who had been twelve days without food, eliminated only 0.000345 per cent. of indican, spectroscopically determined, the ordinary method showing no indican whatsoever.

The fact that high fever is not necessarily accompanied by an increased degree of indicanuria, as pointed out by Jaffe already, is also an important factor against Salkowsky's views. Salkowsky, it is true, was unable to confirm the absence of indican from the urine of dogs at least, finding an elimination of $\frac{4}{5}$ mgrm. from the second to the fifth day of starvation, as compared with 17 mgrms. per diem while being fed with meat. (*Ber. der Deutsch. chem. Gesellsch.*, vol. xii. p. 138.)

Von den Velden likewise observed that in a dog which had been without food for five or six days at a time the conjugate sulphates had only diminished to one-half. Jaffe (*loc. cit.*) cites a case of complete occlusion of the œsophagus, owing to the presence of a carcinoma, in which no nourishment had been taken for eight days preceding death, and in which 17 mgrms. of indigo were demonstrated nevertheless on the day of death. As far as the latter case is concerned, a possible source for the indol-production could be sought for in the process of necrosis of the carcinomatous material, a point which Jaffe did not exclude.

For an explanation of Salkowsky's cases it is not necessary to refer the production of indol during starvation to a decomposition of pancreatic tissue, referable to the activity of micro-organisms located in the pancreas, according to Tiegel and Billroth (Virchow's *Archiv*, vol. lx. p. 453), and as suggested by Weiss (Ibid., vol. lxx. p. 80), but a very much more probable source for the production of indol in these conditions we find in the so-called "Hungerkoth," secreted by the intestinal mucous membrane, according to Voit, to the amount of 0.66–6.4 grammes residue, with 5.04–7.96 per cent. of nitrogen. The question may, however, still be asked, Why is it that Salkowsky was able to demonstrate indican in the urine of starving dogs, while in starving man no indican has been observed? An explanation of this apparent incongruity may be found in the experiments of Mueller (*loc. cit.*), which appear to indicate quite conclusively that the conditions in man and animals cannot be alike during hunger.

The final blow, however, which Salkowsky's theories received came from Baumann, who succeeded in absolutely disinfecting the intestinal tract in a dog by means of large doses of calomel, when all traces of indican, and for that matter of phenol and paracresol, dissappeared from the urine. The more recent experiments from Baumann's laboratory finally fully confirm the view that indol in health and disease is only formed in the intestines, provided that resorption of decomposing pus is not taking place in any part of the body, in which case a second source of indol and a corresponding indican-formation would exist.

What has thus been shown to be true for indol, viz., indican, is likewise true for phenol and paracresol, etc.; in other words, for all the known conjugate sulphates occurring in the urine, so that the degree of intestinal putrefaction may be directly measured by the elimination of these bodies in the urine. Any factor, then, that will bring about an increased degree of intestinal putrefaction will at the same time call forth an increased elimination of conjugate sulphates.

The question now naturally suggests itself: What is it that keeps the degree of intestinal putrefaction in what may be considered as the physiological limits?

There appears to be but little doubt at the present time that the free hydrochloric acid of the gastric juice is the active agent in this direction.

The Abbé Spalanzani, already (*Experiences sur la digestion.* Trans. by Senebier, new edition, Genève, 1784, pp. 94, 97, 145, 320–330, cit. by Bunge in his *Physiol. und pathol. Chemie,* 1889, 2d ed.; German translation, also, Leipzig, 1875), more than one hundred years ago, had observed antifermentative properties in the gastric juice. Small pieces of meat, covered with gastric juice, resisted putrefaction for days, while such as were left exposed to the air, when only covered with water, very soon emitted a most offensive odor. Spalanzani similarly observed a snake that had swallowed a lizard, and upon opening the stomach of the same sixteen days later the lizard, of course, was found partly digested, but manifesting no odor that could possibly be referred to putrefactive processes. A truly germicidal action on the part of the gastric juice was likewise observed by Spalanzani, for when he introduced meat already undergoing the process of putrefaction into the stomach of certain animals, this meat very soon had lost its putrefactive properties.

That the gastric juice thus possesses very marked antiseptic and germicidal properties is thus very apparent, and, remembering the fact that the mineral acids must be reckoned among the most powerful antiseptics, the supposition that the antiseptic properties of the gastric juice are referable to the presence of free hydrochloric acid appears very justifiable.

Sieber, working under Nencki (*Journ. für prakt. Chemie,* 1879, vol. xix. p. 433), showed, as a matter of fact, that when 50 grammes of hashed meat were exposed to the open air, with 300 c.cm. of 0.1 per cent. of hydrochloric acid, cocci and bacteria were observed in small numbers only after twenty-four hours, while with 0.25 per cent. a few quiescent organisms were only observed on the seventh day, and with 0.5 per cent. there was no sign whatsoever of putrefaction on the seventh day.

Micquel arrived at similar results (*Cbl. für allgemeine, Gesundheitspflege,* 1884, vol. ii. p. 403), finding that 0.2–0.3 gramme of a mineral acid suffices for the purpose of preventing putrefaction in 100 c.cm. of bouillon.

Schmidt (Bidder und Schmidt, *Die Verdaungssaefte und der Stoffwechsel, Mitau,* Leipzig, 1852, pp. 44, 45) determined the amount of free hydrochloric acid in the gastric juice of the dog as 0.25–0.42 per cent., with 0.33 as an average.

Dionys Szabo in Hoppe-Seyler's laboratory (*Zeitsch. für physiol.*

Chemie, 1877, vol. i. p. 155) found 0.3 per cent. in man. In other words, we find a degree of acidity in the gastric juice referable to free hydrochloric acid that has been shown to be necessary for the prevention of putrefactive processes.

Bunge (*Phys. und path. Chem.,* 2te Aufl., 1889) strongly advocates this function of the stomach, and in fact regards it as its most important one.

Granting the correctness of this hypothesis, an increased degree of intestinal putrefaction (a certain degree will, of course, exist in consequence of the development of certain spores that have not been destroyed by the action of the gastric juice) should of course result whenever the acidity of the gastric juice falls below a certain level or is entirely annihilated. Such has actually been found to be the case.

Kast ("Ueber die quantitative Bemessung der antiseptischen Leistung des Magensaftes." Festsch. zur Eroeffnung des neuen allgem. Krankenhauses, Hamburg, 1889, ref. to in Maly's *Jahresb.,* 1889, p. 271) working in Baumann's laboratory was able to demonstrate a largely increased elimination of conjugate sulphates, following the neutralization of the acid gastric juice with large doses of bicarbonate of sodium, as is evident from the following tables:

1. NORMAL DAYS.[1]

C.CM.	H_2SO_4 in 50 c.cm. as $NaSO_4$.		In 24 hours as $NaSO_4$.		
	A.	B.	A.	B.	A : B.
1500	0.1545	0.0100	4.635	0.3	15.4
1700	0.1140	0.0110	3.960	0.374	10.3
1800	0.1100	0.0668	3.960	0.244	16.1
1700	0.1045	0.0085	3.553	0.289	12.5

2. FROM NOW OFF 13 GRMS. OF BICARBONATE OF SODIUM DAILY.

C.CM.	H_2SO_4 in 50 c.cm. as $NaSO_4$		In 24 hours as $NaSO_4$.		
	A.	B.	A.	B.	A : B.
2000	0.0810	0.0213	3.240	0.852	3.8
1900	0.0667	0.0138	2.534	0.524	4.8
2100	0.0567	0.0195	2.381	0.819	2.9
1820	0.1450	0.0225	5.221	0.846	6.1

To these experiments of Kast, v. Noorden (*Zeitsch. für klinische Med.,* vol. xvii.) objected upon the grounds that in the experiments of Kast abnormal conditions had been established in consequence of the introduction of large amounts of alkalies, a much more favorable basis for the development and resorption of putrefactive products, viz., for the formation of conjugate sulphates, being thereby given than is usually to be found in the mere absence of free hydrochloric acid, basing his conclusions upon experiments made in a series of patients where, in the absence of free hydrochloric acid, but with a normal motility of the stomach, a decided increase in the elimination of conjugate sulphates was not observed, the relation of A : B in his cases being the following:

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[1] "A" indicates the amount of mineral sulphates; "B" that of the conjugate sulphates.

	1	2	3	4	5	6	7	8
A : B . .	17.9	12.4	7.6	13.8	5.1	10.5	4.8	11.2

An observation furthermore has been made by Boas (*Deutsch. med. Woch.*, 1891, No. 28) in a case of duodenal stenosis, in which succus entericus was constantly present in the stomach; where gastric juice could thus be definitely excluded; where the relation of A : B was found to vary between 21.9 and 5.36.

The experiments of Mester, however (Inaugural Diss., 1893, and *Zeitsch. für klinische Med.*, vol. xxiv. pp. 441–457), in which the objectionable features of those of Kast were eliminated gave rise to the same conclusion. Mester's conclusions may be summarized as follows: Intestinal putrefaction is brought about normally by the entrance of putrefactive organisms into the digestive tract together with the food, the intensity of the same depending upon the amount of free hydrochloric acid present. It is thus increased in the absence of free hydrochloric acid, which becomes the more evident when putrid meat, less so, when meat carrying but a small number of putrefactive organisms, serves as nourishment, while with a normal amount of free hydrochloric acid, even within wide limits, such differences in the quality of the food remain without influence upon the process of digestion.

Equally suggestive were the observations of Wasbutzki (*Arch. für. exp. Path. und Pharmak.*, vol. xxvi.), the result of which is the following: In cases of intense bacterial fermentation in the stomach an increased elimination of conjugate sulphates results, the cases being such of subacidity or anacidity of the gastric juice; a diminished elimination of conjugate sulphates, on the other hand, was noted in cases of torular fermentation, *i. e.*, such in which hyperacidity and even hypersecretion existed. Two interesting exceptions to this general rule are recorded by Wasbutzki, in both of which a normal and even a diminished elimination of conjugate sulphates was found, associated with anacidity and a simultaneous occurrence of fermentative processes. In both cases much lactic acid and butyric acid were found, and Wasbutzki expresses the opinion that the abnormal quantities of acid in these cases were able to carry on the functions of the free hydrochloric acid, an observation which I have been able to confirm in several cases, and an explanation with which I am inclined to agree.

The cases of Biernacki (*Deutsches Arch. für klin. Med.*, vol. lxix.), finally, in which an increased degree of intestinal putrefaction was found to be associated with a deficiency in the amount of free hydrochloric acid in cases of chronic Bright's disease, likewise support the view that the elimination of conjugate sulphates must be regarded not only as an index of the degree of intestinal putrefaction, but also of the acidity of the gastric juice, or rather of the amount of free acid contained in the same.

Unfortunately, however, it will probably be but very rarely that a quantitative estimation of the total and conjugate sulphates can be carried out by the practising physician, one single determination requiring at least from five to six hours of time, the use of delicate scales, etc.

The question, hence, naturally suggested itself: Does the amount of free hydrochloric acid in the gastric juice affect the indol-producing organisms in exactly the same manner as the phenol-producers, for example? In other words, is an increased elimination of indican from the urine, referable to subacidity or anacidity of the gastric juice, invariably associated with a similar increase of the phenol sulphate—for the others, occurring in mere traces, need not be considered at all in this connection—or are there cases in which increased or diminished indicanuria is associated with diminished or increased phenoluria respectively?

Were an increased elimination of indican invariably associated with an increased elimination of phenol, and a diminished elimination of indican with a diminished elimination of phenol, it is apparent that in that case a quantitative estimation of either would be sufficient for the purpose of deciding the question whether hyperacidity, a normal acidity, subacidity, or anacidity of the gastric juice exists.

While formerly Salkowsky (*Virchow's Archiv*, vol. lxxiii. p. 409) taught that urines rich in indican were at the same time also rich in phenol, there seems to be some doubt as to the correctness of this view, according to Brieger (*Zeitsch. für physiol. Chemie*, vol. ii. p. 256), and the following cases taken from Brieger may serve as an illustration:

CASE IX.—R., aged fifty-four years, suffered for ten years from chronic gastritis (loss of appetite, nausea without vomiting) and anæmia of considerable severity; without the existence of a true cachexia, however; in the beginning bromine-water only occasioned a slight turbidity in the distillate of the urine, while later on, when the patient had improved, his appetite having returned, 0.0223 gramme of tribromophenol, equivalent to 0.0061 gramme of phenol, was obtained from the urine of twenty-four hours. A considerable amount of indican was, however, present.

The same may be said of Case X., also the subject of chronic gastritis, in which only traces of phenol were found.

In Case XI., associated with increased indicanuria, 0.0030 gramme of phenol was found, the case being one of ulcer of the stomach.

In Case XII., also one of ulcer, the amount of phenol varied from 0.0152 to 0.0135 gramme.

Increased indicanuria, associated with an amount of phenol varying from 0.0174 to 0.0337 in one case of cancer of the stomach, and 0.0344 to 0.1130 gramme in another, was likewise observed (Cases XIII. and XIV.).

Later on it appears that Salkowsky himself changed his opinion, so that it may now be regarded as a settled point that increased indicanuria is not necessarily accompanied by increased phenoluria.

The question now suggested itself: Does a diminished elimination of indican in digestive diseases ever accompany an increased elimination of phenol?

This question, as far as my own experiments go, I think I can definitely answer in the negative, for not in a single case in which I was able to demonstrate a diminished elimination of indican have I been able to determine the existence of increased phenoluria, excepting cases in which an active resorption of decomposing pus was taking place from any of the large body-cavities.

An increased phenoluria, on the other hand, not infrequently accompanies an increased indicanuria, and this is especially the case in cases of cancer of the stomach, and also quite constantly observed in cases of general peritonitis and ileus, but of these conditions it is not at present my object to speak.

Having thus determined the fact that an increased elimination of indican may or may not be accompanied by an increased elimination of phenol in digestive diseases, and that a diminished elimination of indican under the same conditions is not accompanied by an increased elimination of phenol, the conclusion that the increased degree of intestinal putrefaction in cases of subacidity and anacidity of the gastric juice is largely due to an increased formation of indol, and that *the indican elimination may hence be regarded as running a course parallel to the degree of antiseptic—viz., germicidal—activity of the gastric juice,* i. e., *the amount of free hydrochloric acid, appears to suggest itself.*

The correctness of this view I have been able to test in a very large number of instances that have fallen under my observation in the course of the last three years.

The gastric juice, it is true, could not be examined in every individual case; the records of those, however, in which this was done and the histories of the others, I think, will be fully convincing, and call for a repetition of my experiments, leading, I hope, to the general adoption of the hypothesis herein set forth, and the general acceptance in practice of so simple a method to obtain an insight into the condition of the gastric juice and the degree of intestinal putrefaction.

I do not wish to convey the impression, however, that with the adoption of this method the use of the gastric tube for diagnostic purposes should be abandoned. From a careful analysis of the urine, it is true, many points of undoubted value can be obtained regarding the condition of stomach and small intestine, etc., but nevertheless the information thus obtained cannot as yet be so complete as that furnished by a direct examination of the stomach contents. *As confirmatory evidence, however, and as a method to be employed where for any reason the use of the tube is either contraindicated or impractical, the same, I am sure, will be found to be of decided value.*

(To be continued.)

NEURALGIA OF THE RIGHT TRIGEMINAL NERVE OF EIGHT YEARS' DURATION;

EXCISION OF THE THREE DIVISIONS AT THE GASSERIAN GANGLION; RECOVERY, WITH PARTIAL DESTRUCTION OF THE GANGLION.

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History and Examination by J. T. Eskridge, M.D.

James L., aged forty-five years, born in Ireland, single, engaged as a laboring miner in Colorado eighteen years, has been suffering from neuralgia of the right trigeminal nerve since March, 1885. His father was very intemperate in his youth; his mother died in childbirth. No nervous or mental diseases in the family. One brother died of consumption. In childhood the patient's health was excellent. He denies syphilis and alcoholism. Fifteen years ago he suffered from what his physician called scurvy. He had been living on salted food, and his feet and legs swelled, and he was weak. In 1883 he had an attack of typhoid fever. From 1883 to 1885 he suffered from rheumatic pains in joints while working under ground in wet mines. In February, 1885, he had a severe attack of rheumatism, with swollen and painful joints. The wrist, elbow, shoulder, knee, and hip-joints were involved. In March, 1885, he began to have pain in the region of the right inferior dental nerve. The attack was extremely severe for three weeks, and after this the pain was constant, but not so severe. The pain was limited to this nerve. Within a year from the time the neuralgia first began it had extended to the region of the face in front of the right ear, and involved an area there one or two inches in diameter. After the extension of the pain to the region of the right ear it became intermittent. He would suffer for a few days from severe pain in the inferior dental nerve, the next day from a dull pain in front of the right ear, when he would be free from pain for several days. The pain in 1889 occasionally extended to the superior maxillary nerve. The first division of the fifth cranial nerve was never involved. At this time the pain became constant again, with periods of severe exacerbation. Before this time he